111-1090

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re U.S. Patent No. 4,290,962 — 06/024,111

Copy No. 1

Issued: September 22, 1981

Box Patent Ext.

To: Yasuhide Tachi; Kazuhiko Michishita;
Jozi Nakagami; Jiro Sawada;
Mitsunori Washitake; and
Yoshiaki Kamano

For: NOVEL HYDROCORTISONE DERIVATIVE

* * * * *

April 25, 1997

SUBMISSION OF APPLICATION FOR EXTENSION OF PATENT TERM UNDER 35 U.S.C. §156

Hon. Commissioner of Patents & Trademarks
Washington, D.C. 20231

Sir:

Submitted herewith are the following papers in support of an application for extension of patent term pursuant to 35 U.S.C. § 156 with respect to the subject patent, filed on behalf of Taisho Pharmaceutical Co., Ltd., a corporation organized under the laws of Japan, having its principal office and place of business in Tokyo, Japan (hereinafter "Applicant"), which is the owner of all right, title and interest in said patent:

1. Power of Attorney from Taisho Pharmaceutical Co., Ltd. to, *inter alia*, the undersigned. (It should be noted that the Power of Attorney submitted with original Copy No. 1 of these papers is the originally executed Power of Attorney.)

2. Application for Extension of Patent Term Under 35 U.S.C. § 156, including:

   Exhibit 1 - Package insert describing the approved product; and

   Exhibit 2 - Copy of the subject patent.

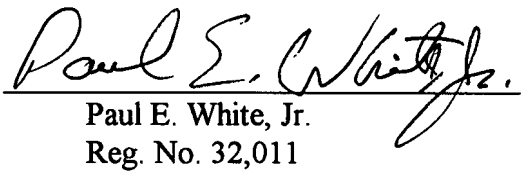
3. Declaration of Paul E. White, Jr., Applicant's patent counsel.

4. Certificate that these application papers are being submitted in duplicate.

5. Check in the amount of $1,090.00 (37 C.F.R. § 1.20(j)(1)) payable to the Commissioner of Patents and Trademarks to cover the prescribed fee.

Respectfully submitted,

CUSHMAN DARBY & CUSHMAN
Intellectual Property Group of
PILLSBURY MADISON & SUTRO, LLP

By: 

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IN THE UNITED STATES PATENT AND TRADEMARK OFFFICE

U.S. Patent No. 4,290,962

Issued: September 22, 1981

To: Yasuhide Tachi; Kazuhiko Michishita;
Jozi Nakagami; Jiro Sawada;
Mitsunori Washitake; and
Yoshiaki Kamano

For: NOVEL HYDROCORTISONE DERIVATIVE

* * * * *

POWER OF ATTORNEY FROM ASSIGNEE

Hon. Commissioner of Patents & Trademarks
Washington, D.C. 20231

Sir:

The undersigned Taisho Pharmaceutical Co., Ltd. being the assignee of record in the above-identified patent, hereby appoints Paul E. White, Jr. (Reg. No. 32,011), Paul N. Kokulis (Reg. No. 16,773) and Donald J. Bird (Reg. No. 25,323) of the firm Pillsbury Madison & Sutro, L.L.P. (Cushman Darby & Darby Intellectual Property Group), Ninth Floor, 1100 New York Avenue, N.W., Washington D.C. 20005-3918, telephone number (202) 861-3000 (to whom all communications about this patent are to be directed), individually and collectively, our attorneys to transact all business in the Patent and Trademark Office in connection therewith, including specifically, but not limited to, the filing on our behalf of any application for extension of the patent term thereof under 35 USC 156.

TAISHO PHARMACEUTICAL CO., LTD.
Assignee

By 
Name: Akira Uehara

Title: President

April 14, 1997
Date

IN THE UNITED STATES PATENT AND TRADEMARK OFFFICE

Box Patent Ext.

In re U.S. Patent No. 4,290,962

Issued: September 22, 1981

To: Yasuhide Tachi; Kazuhiko Michishita;
Jozi Nakagami; Jiro Sawada;
Mitsunori Washitake; and
Yoshiaki Kamano

For: NOVEL HYDROCORTISONE DERIVATIVE

* * * * *

April 25, 1997

APPLICATION FOR EXTENSION OF PATENT TERM
UNDER 35 U.S.C. §156

Hon. Commissioner of Patents & Trademarks
Washington, D.C. 20231

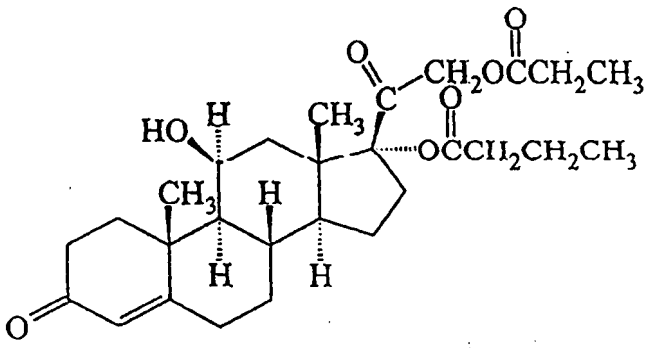
Sir:

Taisho Pharmaceutical Co., Ltd., a corporation organized under the laws of Japan, having its principal office and place of business in Tokyo, Japan (hereinafter "Applicant") is the owner of the entire interest in and to Letters Patent of U.S. Patent No. 4,290,962 (hereinafter "the Patent") granted to Yasuhide Tachi, Kazuhiko Michishita, Jozi Nakagami, Jiro Sawada, Mitsunori Washitake, and Yoshiaki Kamano for NOVEL HYDROCORTISONE DERIVATIVE by reason of an assignment to Applicant recorded in the United States Patent and Trademark Office on March 3, 1981, at Reel 3830, Frame 0135.

Applicant, through the undersigned counsel, hereby applies for a three year (1,096 days) extension of the term of United States Patent No. 4,290,962 under 35 U.S.C. §156 on the basis of the following information submitted in accordance with the provisions of Title 37 C.F.R. §1.740(a) (1)-(17), set forth in the sequence of those subparagraphs. Filed herewith is a Power of Authority authorizing the undersigned to file and prosecute this Application for Extension of Patent Term, and to transact all business in relation thereto.

(1) This application for extension is based upon the regulatory review period before the U.S. Food and Drug Administration (FDA) of Applicant's approved product, "PANDEL Cream", a pharmaceutical formulation of hydrocortisone buteprate. Hydrocortisone buteprate is:

11β, 17,21-trihydroxypregn-4-ene-3,20-dione 17-butyrate 21-propionate (corresponding to 17α-butyryloxy-11β-hydroxy-21-propionyloxy-4-pregnen-3,20-dione, as claimed in the Patent), and has the structural formula:



Hydrocortisone buteprate is indicated for the relief of the inflammatory and pruritic manifestations of dermatoses, as is more particularly described in the package insert attached hereto as EXHIBIT 1.

(2) The approved product was subject to regulatory review under Section 505(b) of the Federal Food, Drug and Cosmetic Act (21 U.S.C. §355).

(3) The approved product "PANDEL Cream" received permission for commercial marketing or use after a regulatory review period under Section 505(b) of the Federal Food, Drug and Cosmetic Act (21 U.S.C. §355) on February 28, 1997.

(4) The active ingredient in the approved product "PANDEL Cream" is hydrocortisone buteprate. To the best of Applicant's knowledge, the permission for the commercial marketing or use of this product after such regulatory review period is the first permitted commercial marketing or use of such product under the Federal Food, Drug and Cosmetic Act and it has not been previously approved for commercial marketing or use under the Federal Food, Drug, and Cosmetic Act, the Public Health Service Act, or the Virus-Serum-Toxin Act.

(5) This application for extension of patent term under 37 C.F.R. §1.720(f) is being submitted within the permitted 60 day period, which period will expire on April 29, 1997.

(6) The patent for which an extension is being sought is as follows:

U.S. Patent No. 4,290,962

Issued: September 22, 1981

Expires: March 26, 1999

Inventors: Yasuhide Tachi; Kazuhiko Michishita; Jozi Nakagami; Jiro Sawada; Mitsunori Washitake; and Yoshiaki Kamano

For: NOVEL HYDROCORTISONE DERIVATIVE

(7) A copy of the patent for which an extension is being sought, including the entire specification and claims, is attached as EXHIBIT 2.

(8) There is no disclaimer, certificate of correction or reexamination certificate in the subject patent, and it is not subject to maintenance fee payments.

Applicant is the owner of all right, title and interest in two additional patents relating to the approved product: U.S. Patent No. 4,794,106, directed to a cream formulation of the hydrocortisone buteprate; and U.S. Patent No. 4,794,107, directed to an ointment formulation of the hydrocortisone buteprate.

(9) U.S. Patent No. 4,290,962, for which this extension is sought, claims in claim 1, the compound hydrocortisone 17-butyrate 21-propionate. Claim 1 specifically relates to the approved product "PANDEL Cream", as described in more detail below:

CLAIM 1. 17α-butyryloxy-11β-hydroxy-21-propionyloxy-4-pregnen-3,20-dione.

Hydrocortisone buteprate, the active ingredient of the approved product "PANDEL Cream" as indicated in the approved package insert, EXHIBIT 1, is the compound of claim 1.

(10) The relevant dates and information pursuant to 35 U.S.C. 156(g) in order to enable the Secretary of Health and Human Services to determine the applicable regulatory review period are as follow:

(a) Issue date of the patent: September 22, 1981

(b) Effective date of IND application no. 27,038:

filed (received) September 6, 1985

effective October 6, 1985

(c) Expiration date of the patent March 26, 1999

(d) NDA 20-453 - submitted March 1, 1994

(e) NDA 20-453 - approved February 28, 1997

(11) A brief description of the significant activities undertaken by or on behalf of the Applicant during the applicable regulatory review period with respect to the approved product, and the significant dates applicable to such activities, are set forth below:

March 1, 1994	NDA is submitted to FDA.
April 28, 1994	FDA teleconference to avoid receipt of Refusal to File letter. The major issue is the clinical program to obtain topical corticosteroid class labeling.
May 6, 1994	NDA is amended to limit labeling to treatment of atopic dermatitis only.
September 22, 1994	NDA is amended with data requested during FDA teleconference on May 28, 1994 (included translations of all foreign inserts and worldwide safety data).
November 2, 1994	FDA sends first not approvable letter.
July 27, 1995	Amendment submitted in response to November 1, 1994 deficiency letter.
September 18, 1995	Meeting at FDA offices in Rockville, MD, clarified all open issues. FDA had determined that a submitted Danish atopic dermatitis study was not sufficient and could not qualify as a second study. Since a second psoriasis study was near completion, FDA agreed to accept two psoriasis studies and one atopic dermatitis study for class labeling (psoriasis

	being the more difficult to treat).
January 5, 1996	Submission of amendment including psoriasis study and revision to class labeling (Numerous telephone amendments primarily in the period between February and July, 1996).
July 11, 1996	"Approvable" letter received requesting updated worldwide safety data and labeling changes.
July 23, 1996	FDA is notified of intent to amend NDA to address the issues contained in the July 11, 1996 "approvable" letter.
August 30, 1996	NDA is amended to revise the specifications for the inactive ingredient raw material, glyceryl stearate SE non NF.
October 3, 1996	Amendment is submitted responding to the July 11, 1996 "approvable" letter.
December 18, 1996	Due to the protracted time since submission of the October 3, 1996 amendment, the FDA is sent correspondence agreeing to all conditions set forth in the July 11, 1996 "approvable" letter.
February 28, 1997	NDA "approval" letter (sent by FDA via telefax on March 3, 1997).

(12) Applicant is of the opinion that U.S. Patent No. 4,290,962 is eligible for extension under 35 U.S.C. §156 because it satisfies all the requirements for such extension inasmuch as:

(i) such patent claims the human drug product hydrocortisone buteprate (35 U.S.C. §156(a));

(ii) the term of such patent has not expired before the submission of this application(35 U.S.C. §156(a)(1));

(iii) the term of such patent has never been extended (35 U.S.C. §156(a)(2));

(iv) the application for extension is submitted by the owner of record, through the undersigned counsel, in accordance with the requirements of 35 U.S.C. §156(d);

(v) the approved product, "PANDEL Cream" or hydrocortisone buteprate, has been subject to a regulatory review period before its commercial marketing or use (35 U.S.C. §156(a)(4));

(vi) the permission for commercial marketing or use of the product, "PANDEL Cream" or hydrocortisone buteprate, after the regulatory review period, is the first permitted commercial marketing or use of the approved product under the provisions of the Federal Food, Drug and Cosmetic Act (21 U.S.C. §355) under which such regulatory review period occurred; and

(vii) no other patent has been extended for the same regulatory review period for the product "PANDEL Cream" or hydrocortisone buteprate (35 U.S.C. §156(c)(4)).

Applicant requests an extension of the patent term of U.S. Patent No. 4,290,962 by three years (1,096 days) from the original expiration date of March 26, 1999 to March 26, 2002. This period of extension is calculated according to the following subsections of 37 C.F.R. §1.775:

(a) Because the Patent was in force on June 8, 1995, under 35 U.S.C. §154(c)(1), the original expiration date of the Patent is 20 years from the application filing date, that is March 26, 1999 (the longer of: 20 years from the application filing date, i.e., March 26, 1999 compared to 17 years from date of issue, i.e., September 22, 1998).

(b) The length of the regulatory review period was 1,096 days.

(c) The regulatory review period of 1,096 days is calculated as the sum of:

(1) No exemption request under section 505 or section 507 of the Federal Food, Drug, and Cosmetic Act was submitted by Applicant, so this paragraph is not applicable; and

(2) The number of days in the period beginning on the date the application was initially submitted from the approved product under subsection (b) of section 505 of the Federal Food, Drug, and Cosmetic Act and

ending on the date such application was approved under such section, that is from March 1, 1994 to February 28, 1997 is **1,096 days**.

(d) The term of the patent as extended for a human drug product is 1,096 days as determined by:

(1) subtracting from the number of days in the regulatory review period of 1,096 days the following:

(i) None of the periods of paragraphs (c)(1) and (c)(2) were on and before the date on which the patent issued (September 22, 1981), so this paragraph is not applicable;

(ii) The Applicant acted with due diligence in the periods of paragraphs(c)(1) and (c)(2), so this paragraph is not applicable;

(iii) No exemption application was submitted under paragraph (c)(1), so this paragraph is not applicable;

(2) The number of days in paragraph (d)(1) is 1,096 days and thus the original term of the Patent plus 1,096 days is March 26, 2002;

(3) Adding 14 years to the date of approval of the NDA (February 28, 1997) results in a date of February 28, 2011;

(4) The earlier of the dates calculated under paragraphs (d)(2) and (d)(3) is March 26, 2002;

(5) The original patent was not issued after September 24, 1984, so this paragraph is not applicable;

(6) The original patent was issued before September 24, 1984.

(i) No request was submitted for an exemption before September 24, 1984, therefore:

(A) add 5 years to the original expiration date of the Patent (March 26, 1999) to result a date of March 26, 2004;

(B) the earlier of the dates obtained pursuant to paragraphs (d)(4) and (d)(6)(i)(A) is **March 26, 2002**.

(ii) A request was not submitted for an exemption before September 24, 1984 and thus this paragraph is not applicable.

(13) Applicant, through its undersigned counsel, acknowledges a duty to disclose to the Commissioner of Patents and Trademarks and the Secretary of Health and Human Services any information which is material to the determination of entitlement to extension sought, in accordance with 37 C.F.R.§1.765.

(14) A check in the amount of $1,090, payable to the Commissioner of Patents and Trademarks is attached to cover the fee prescribed by 37 C.F.R.§1.20(j)(1) for receiving and

acting upon this application for extension. The Commissioner is hereby authorized to charge any deficiency, or credit any surplus, in the amount indicated above relative to the required fee to our Account No. 03-3975, Order No. 11453/224557.

(15) Please send all inquiries and correspondence relating to this application for patent term extension to:

Paul E. White, Jr.
Pillsbury Madison & Sutro LLP
Cushman Darby & Cushman
Intellectual Property Group
1100 New York Avenue, N.W.
Ninth floor, East Tower
Washington, D.C. 20005-3918

(16) Submitted herewith is a certification that these application papers are being submitted in duplicate.

(17) Additionally submitted herewith is a declaration of Paul E. White, Jr. As patent counsel for Applicant pursuant to 37 C.F.R.§1.740(b)(1) as authorized by the Power of Attorney executed by the Applicant submitted herewith.

Respectfully submitted,

CUSHMAN DARBY & CUSHMAN
Intellectual Property Group of
PILLSBURY MADISON & SUTRO, LLP

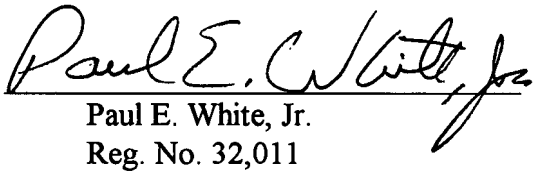
By: 

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EXHIBIT 1

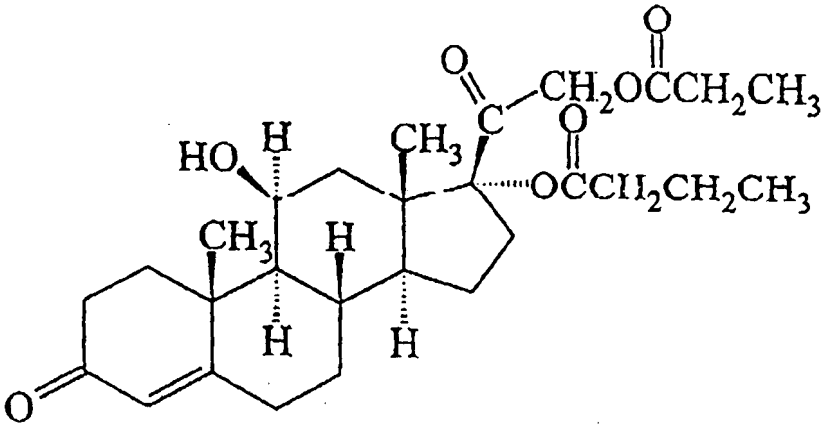
NDA 20-453
Rev. Date: 2-25-97

PANDEL® (hydrocortisone buteprate cream) Cream, 0.1 %[1] For Dermatologic Use Only Not For Ophthalmic Use

DESCRIPTION

PANDEL Cream contains hydrocortisone buteprate, a synthetic adrenocorticosteroid, for dermatologic use. The topical corticosteroids constitute a class of primarily synthetic steroids used as anti-inflammatory and anti-pruritic agents.

Hydrocortisone buteprate is a tasteless and odorless white crystalline powder practically insoluble in hexane or water, slightly soluble in ether, and very soluble in dichloromethane, methanol and acetone. Chemically, it is 11β,17,21-trihydroxypregn-4-ene-3,20-dione 17-butyrate 21-propionate. The structural formula is:



Molecular Formula: $C_{28}H_{40}O_7$ Molecular Weight: 488.62

Each gram of PANDEL (hydrocortisone buteprate cream) Cream, 0.1% contains: 1 mg of hydrocortisone buteprate in a cream base of propylene glycol, white petrolatum, light mineral oil, stearyl alcohol, polysorbate 60, sorbitan monostearate, glyceryl monostearate, PEG-20 stearate, glyceryl stearate, methylparaben, butylparaben, citric acid, sodium citrate anhydrous, and purified water.

CLINICAL PHARMACOLOGY

Topical corticosteroids share anti-inflammatory, anti-pruritic and vasoconstrictive actions. The mechanism of anti-inflammatory activity of the topical corticosteroids is unclear. However, corticosteroids are thought to act by the induction of phospholipase A_2 inhibitory proteins, collectively called lipocortins. It is postulated that these proteins control the biosynthesis of potent mediators of inflammation such as prostaglandins and leukotrienes by inhibiting the release of their common precursor arachidonic acid. Arachidonic acid is released from membrane phopholipids by phospholipase A_2.

Pharmacokinetics: The extent of percutaneous absorption of topical corticosteroids is determined by many factors, including the vehicle and the integrity of the epidermal barrier. Use of occlusive dressings with hydrocortisone for up to 24 hours has not been shown to increase penetration; however, occlusion of hydrocortisone for 96 hours does markedly enhance penetration. Topical corticosteroids can be absorbed from normal intact skin. Inflammation and/or other disease processes in the skin increase percutaneous absorption.

Studies performed with Pandel (hydrocortisone buteprate cream) Cream, 0.1% indicate that it is in the medium range of potency compared with other topical corticosteroids.

INDICATIONS AND USAGE

PANDEL (hydrocortisone buteprate cream) Cream, 0.1% is a medium potency corticosteroid indicated for the relief of the inflammatory and pruritic manifestations of corticosteroid-responsive dermatoses in patients 18 years of age or older.

CONTRAINDICATIONS

PANDEL (hydrocortisone buteprate cream) Cream, 0.1% is contraindicated in those

patients who are hypersensitive to hydrocortisone buteprate or to any of the components of the preparation.

PRECAUTIONS

General: Systemic absorption of topical corticosteroids can produce reversible hypothalamic-pituitary-adrenal (HPA) axis suppression with the potential for glucocorticosteroid insufficiency after withdrawal of treatment. Manifestations of Cushing's syndrome, hyperglycemia, and glucosuria can also be produced in some patients by systemic absorption of topical corticosteroids while on treatment.

Patients applying a topical steroid to a large surface area or to areas under occlusion should be evaluated periodically for evidence of HPA-axis suppression. This may be done by using the ACTH stimulation, A.M. plasma cortisol or urinary free cortisol tests.

If HPA axis suppression is noted, an attempt should be made to withdraw the drug, to reduce the frequency of application, or to substitute a less potent steroid. Recovery of HPA axis function is generally prompt and complete upon discontinuation of the drug. Infrequently, signs and symptoms of steroid withdrawal may occur, requiring supplemental systemic corticosteroids. For information on systemic supplementation, see prescribing information for those products.

Pediatric patients may be more susceptible to systemic toxicity from equivalent doses due to their larger skin surface to body mass ratios. (See **PRECAUTIONS-Pediatric Use**).

If irritation develops, Pandel (hydrocortisone buteprate cream) Cream, 0.1% should be discontinued and appropriate therapy instituted. Allergic contact dermatitis with corticosteroids is usually diagnosed by observing a failure to heal rather than noting a clinical exacerbation, as observed with most topical products not containing corticosteroids.

If concomitant skin infections are present or develop, an appropriate antifungal or antibacterial agent should be used. If a favorable response does not occur promptly, use of Pandel (hydrocortisone buteprate cream) Cream, 0.1% should be discontinued until the infection has been adequately controlled.

Information for the patient: Patients using PANDEL (hydrocortisone buteprate cream)

Cream, 0.1% should receive the following information and instructions:

1. This medication is to be used as directed by the physician. It is for external use only. Avoid contact with the eyes.

2. This medication should not be used for any disorder other than that for which it was prescribed.

3. The treated skin area should not be bandaged or otherwise covered or wrapped so as to be occlusive, unless directed by the physician.

4. Patients should report to their physician any signs of local adverse reactions.

5. Parents of pediatric patients should be advised not to use Pandel (hydrocortisone buteprate cream) Cream, 0.1% in the treatment of diaper dermatitis. Pandel (hydrocortisone buteprate cream) Cream, 0.1% should not be applied in the diaper area as diapers or plastic pants may constitute occlusive dressings (See DOSAGE AND ADMINISTRATION).

6. This medication should not be used on the face, underarms, or groin areas unless directed by the physician.

7. As with other corticosteroids, therapy should be discontinued when control is achieved.

If no improvement is seen within two weeks, contact the physician.

Laboratory tests: The following tests may be helpful in evaluating if HPA axis suppression does occur: ACTH stimulation test
A.M. plasma cortisol test
Urinary free cortisol test

Carcinogenesis, Mutagenesis and Impairment of Fertility: Long-term animal studies have not been performed to evaluate the carcinogenic potential or the effect on fertility of topical corticosteroids.

In two mutagenicity experiments using hydrocortisone buteprate, negative responses were observed in the occurrence of micronuclei in the bone marrow of mice and in the Ames reverse mutation test bacterial assay-with and without metabolic activation.

Pregnancy: Teratogenic Effects - *Pregnancy Category C.* Corticosteroids have

been shown to be teratogenic in laboratory animals when administered systemically at relatively low dosage levels. Some corticosteroids have been shown to be teratogenic after dermal application to laboratory animals.

Hydrocortisone buteprate has not been tested for teratogenicity when applied topically; however, it is absorbed percutaneously, and studies in Wistar rats using the subcutaneous route resulted in teratogenicity at dose levels equal to or greater than 1 mg/kg. This dose is approximately 12 times the human average topical dose of Pandel Cream, 0.1% assuming 3% absorption and an application of 30 g/day on a 70 kg individual. Abnormalities seen included delayed ossification of the caudal vertebrae and other skeletal variations, cleft palate, umbilical hernia, edema, and exencephalia.

In rabbits, hydrocortisone buteprate given by the subcutaneous route was teratogenic at doses equal to or greater than 0.1 mg/kg. This dose is approximately 2 times the human average topical dose of Pandel Cream, 0.1% assuming 3% absorption and an application of 30 g/day on a 70 kg individual. Abnormalities seen included delayed ossification of the caudal vertebrae and other skeletal abnormalities, cleft palate and increased fetal mortality.

The differences between the doses used in animals studies and the proposed human dose may not fully predict the human outcome. The animals received a bolus subcutaneous dose, whereas humans receive a dermal application, where absorption is lower and highly dependent on various factors (e.g., vehicle, integrity of epidermal barrier, occlusion).

There are no adequate and well-controlled studies of the teratogenic potential of hydrocortisone buteprate in pregnant women. Although human epidemiological studies do not indicate an increased incidence of teratogenicity with the use of topical corticosteroids, Pandel Cream should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Nursing Mothers: Systemically administered corticosteroids appear in human milk and could suppress growth, interfere with endogenous corticosteroid production, or cause other untoward effects. It is not known whether topical administration of corticosteroids could result in sufficient systemic absorption to produce detectable quantities in human milk. Because many drugs are excreted in human milk, caution should be exercised when Pandel (hydrocortisone buteprate cream) Cream, 0.1% is administered to a nursing woman.

Pediatric Use: Safety and effectiveness in pediatric patients have not been established. Because of a higher ratio of skin surface area to body mass, pediatric patients are at a greater risk than adults of HPA axis suppression and Cushing's syndrome when they are treated with topical corticosteroids. They are therefore also at a greater risk of adrenal insufficiency during and/or after withdrawal of treatment. Adverse effects including striae have been reported with inappropriate use of topical corticosteroids in infants and children.

Hypothalamic-pituitary-adrenal (HPA) axis suppression, Cushing's syndrome, linear growth retardation, delayed weight gain, and intracranial hypertension have been reported in children receiving topical corticosteroids . Manifestations of adrenal suppression in children include low plasma cortisol levels and an absence of response to ACTH stimulation. Manifestations of intracranial hypertension include bulging fontanelles, headaches, and bilateral papilledema.

ADVERSE REACTIONS

The most frequent adverse reactions reported for Pandel (hydrocortisone buteprate cream) Cream, 0.1 % have included burning in 4, stinging in 2, and moderate paresthesia in 1 out of 226 patients.

The following local adverse reactions are reported with topical corticosteroids, and they may occur more frequently with the use of occlusive dressings. These reactions are listed in an approximate decreasing order of occurrence: burning, itching, irritation, dryness, folliculitis, hypertrichosis, acneiform eruptions, hypopigmentation, perioral dermatitis, allergic contact dermatitis, secondary infections, skin atrophy, striae, miliaria.

OVERDOSAGE

Topically applied corticosteroids can be absorbed in sufficient amounts to produce systemic effects. (See **PRECAUTIONS**).

DOSAGE AND ADMINISTRATION

Apply a thin film of PANDEL (hydrocortisone buteprate cream) Cream, 0.1% to the affected area once or twice a day depending on the severity of the condition. Massage gently until the medication disappears.

Occlusive dressings may be used for the management of refractory lesions of psoriasis and other deep-seated dermatoses, such as localized neurodermatitis (lichen simplex chronicus).

As with other corticosteroids, therapy should be discontinued when control is achieved. If no improvement is seen within 2 weeks, reassessment of the diagnosis may be necessary.

Pandel (hydrocortisone buteprate cream) Cream, 0.1 % should not be used with occlusive dressings unless directed by the physician. Pandel (hydrocortisone buteprate cream) Cream, 0.1% should not be applied in the diaper area, as diapers or plastic pants may constitute occlusive dressings.

HOW SUPPLIED

PANDEL (hydrocortisone buteprate cream) Cream, 0.1% a white to off-white opaque cream is supplied as follows:

15 g tubes (NDC 0281-0153-15)
80 g tubes (NDC 0281-0153-80)
45 g tubes (NDC 0281-0153-46)
1.5 g Foilpac (0281-0153-08)

Store at controlled room temperature 15° - 30 °C (59° - 86° F)

CAUTION: Federal law prohibits dispensing without a prescription.

SAVAGE LABORATORIES®
a division of Altana Inc.
MELVILLE, NEW YORK 11747

EXHIBIT 2

United States Patent [19]

Tachi et al.

[11] **4,290,962**

[45] **Sep. 22, 1981**

[54] **NOVEL HYDROCORTISONE DERIVATIVE**

[75] Inventors: **Yasuhide Tachi**, Tokyo; **Kazuhiko Michishita**, Omiya; **Jozi Nakagami**, Hasuda; **Jiro Sawada**, Tokyo; **Mitsunori Washitake**, Omiya; **Yoshiaki Kamano**, Tokyo, all of Japan

[73] Assignee: **Taisho Pharmaceutical Co., Ltd.**, Tokyo, Japan

[21] Appl. No.: **24,111**

[22] Filed: **Mar. 26, 1979**

[30] **Foreign Application Priority Data**

Mar. 29, 1978 [JP] Japan 53-36251

[51] Int. Cl.³ C07J 5/00

[52] U.S. Cl. 260/397.45

[58] Field of Search 260/397.45

[56] **References Cited**

U.S. PATENT DOCUMENTS

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[57] **ABSTRACT**

17α-butyryloxy-11β-hydroxy-21-propionyloxy-4-pregnen-3,20-dione, i.e., hydrocortisone 17-butyrate 21-propionate of the present invention is prepared by acylating hydrocortisone 17-butyrate with propionic acid anhydride or halide. The compound of the present invention has excellent anti-inflammatory effect, percutaneous absorption and less side effect.

1 Claim, No Drawings

NOVEL HYDROCORTISONE DERIVATIVE

BACKGROUND

Various kinds of corticosteroids have recently been used as antirheumatic, anti-inflammatory, anti-allergic and antishock agents. Further, with respect to the administration route, they have recently become widely utilized externally as well as internally. These compounds includes those having a structure in which the corticosteroid is substituted by methyl, hydroxy, halogen(bromine, chlorine or fluorine), esterified hydroxy or acetonised hydroxy, and derivatives thereof. Accordingly, they have structures significantly modified or changed from structures of naturally occurring corticosteroids, such as, for example, triamcinolone, fluorocinolone acetonide, betamethasone, dexamethasone and their derivatives. Although these compounds are clinically effective, they tend to show side effects such as systemic action, and some therapeutists have been concerned about the side effects by the halogen-substituted structure. Furthermore, since each of these prior compounds has a structure considerably modified or changed from natural occurring corticosteroid structures, their mechanisms of metabolism and excretion in a living body are complicated. Accordingly, even if they are externally administered, they are not always safe.

Given such a background for these prior steroids, we have conducted research with a view to developing a steroid having a structure similar to that of a naturally occurring corticosteroid, and showing an excellent anti-inflammatory action on topical administration. As a result, we have found that 17α-butyryloxy-11β-hydroxy-21-propionyloxy-4-pregnen-3,20-dione, i.e., hydrocortisone 17-butyrate 21-propionate, has a much higher optical anti-inflammatory activity than other hydrocortisone derivatives and the commercially available steroidal agents for external administration.

DESCRIPTION AND PREFERRED EMBODIMENTS

The present invention relates to 17α-butyryloxy-11β-hydroxy-21-propionyloxy-4-pregnen-3,20-dione(I).

An object of the present invention is to provide a novel steroid, of a structure similar to naturally occurring corticosteroid structures, having excellent anti-inflammatory and less side effect upon external administration.

The compound(I) of the present invention may be synthesized according to various methods, preferably, according to the following method.

Hydrocortisone is reacted with a compound(II) represented by the general formula

$$CH_3CH_2CH_2C(OR)_3$$

wherein R is lower alkyl containing 1 to 5 carbon atoms, to give the corresponding 17α,21-(1'-alkoxy-1'-propylmethylenedioxy)-11β-hydroxy-4-pregnen-3,20-dione(III).

The cleaving reaction of the compound(III) with an acid such as oxalic acid or a mineral acid such as hydrochloric acid gives hydrocortisone 17-butyrate(IV). The acylation of the compound(IV) at its 21-hydroxy gives the compound(I) of the present invention. The acylation is generally carried out by using an acylating agent such as propionic acid anhydride or halide (bromide or chloride) in a solvent such as chloroform, methylene chloride, tetrahydrofuran, toluene or benzene in the presence of a base such as pyridine or triethylamine according to a conventional method. When an acid anhydride is used, the acylation is generally completed in pyridine in 2 to 3 hours at room temperature. When an acid halide is used, the acylation is, preferably, carried out under cooling at 0° to 10° C. for about 3 to 5 hours. After completion of the acylation, the reaction solution is poured into ice water and extracted with a solvent such as chloroform to give the compound(I). Alternatively, the reaction solution may be directly concentrated under reduced pressure to give the compound(I). The purification of the compound(I) obtained by each method may be carried out by recrystallization or column chromatography.

The compound(I) of the present invention has high topical anti-inflammatory action, and may be used for treatment of mammalian skin diseases such as acute or chronic eczema, seborrhoeic eczema, atopic dermatitis, infantile eczema, contact dermatitis and psoriasis vulgaris. For these purposes the compound(I) is administered topically in conventional dosage forms such as ointments, creams, lotions, liquid coatings, plasteres and powders prepared according to conventional pharmaceutical practice. The compound(I) may be used in the range of 0.01 to 5.0% by weight, preferably, 0.05 to 2.0% by weight in said conventional form.

The compound(I) shows very excellent anti-inflammatory and percutaneous absorption effects superior to those of other diesters of hydrocortisone. It is believed that these prominent effects are due to the types of ester groups at the 17 and 21 positions of hydrocortisone. Namely, although the compound(I) has a structure which is not too far from a natural occurring steroid structure and does not contain such substituents as halogens, the compound(I) has superior anti-inflammatory activity over other derivatives containing such substituents.

Vasoconstrictor test

Petrolatum-based ointments containing 0.1% of the compounds listed in Table 1, respectively, were prepared. These ointments were randomly applied to forearms of healthy adult male volunteers, and then they were removed at 4 hours after application. The degrees of vasoconstriction on the applied sites were recorded at 4 hours after removal of the ointments by four degrees as ++, +, ± and −, which were scored as 3, 2, 1 and 0, respectively. The scores of thirty volunteers for each ointment were summed up. The total and average scores of each test compound are shown in Table 1, wherein the total score is the value of the summed score of each ointment, and the average score is obtained by dividing the total value by the number of the volunteers.

TABLE 1

compound	total score	average score
compound (I)	74	2.47
hydrocortisone 17,21-diacetate	47	1.57
hydrocortisone 17-acetate 21-propionate	50	1.67
hydrocortisone 17-acetate 21-butyrate	10	0.33
hydrocortisone 17-propionate 21-acetate	54	1.80
hydrocortisone 17,21-dipropionate	61	2.03
hydrocortisone 17-propionate 21-butyrate	58	1.93
hydrocortisone 17-butyrate 21-acetate	55	1.83
hydrocortisone 17,21-dibutyrate	47	1.57

TABLE 1-continued

compound	total score	average score
hydrocortisone 17-valerate 21-acetate	58	1.93
hydrocortisone 17-valerate 21-propionate	49	1.63
hydrocortisone 17-valerate 21-butyrate	38	1.27
hydrocortisone 17-butyrate	51	1.70
betamethasone 17-valerate	60	2.00
placebo ointment	2	0.07

Percutaneous absorption test

Percutaneous absorption of the compound(I) was examined using rat normal skin, and compared with those of hydrocortisone and hydrocortisone 17-butyrate.

1.0 ml of an aqueous solution containing 5 μg of the test compound was charged into a short glass tube fixed at an area on the rat abdominal surface (4 cm^2) where the hair was cut off. After the specified time, the recovered amount of the test compound in the residual aqueous solution was determined by high pressure liquid chromatography.

Percutaneous absorption(%) of the test compound is calculated by the following expression

$$\frac{5\ \mu g - \text{Recovered amount } (\mu g)}{5\ \mu g} \times 100$$

and results are shown in Table 2, wherein the mean and its standard error are given for each set of experiments.

TABLE 2

Steroid	Time (hours) 1.0	3.0	5.0	7.0
hydrocortisone	1.8 ±1.4	4.6 ±2.2	5.6 ±2.5	6.5 ±3.1
hydrocortisone 17-butyrate	4.5 ±1.8	7.5 ±2.3	11.4 ±3.8	14.1 ±4.2
compound (I)	10.8 ±4.2	14.7 ±3.1	28.0 ±4.7	43.4 ±5.7

Subacute toxicity test

The subacute toxicity of the compound(I) when it was administered to Wistar strain rats by the subcutaneous route consecutively for 30 days was investigated in contrast with hydrocortisone 17-butyrate and betamethasone 17-valerate, under the same experimental conditions. The test compounds were suspended in 5% gum arabic in appropriate concentrations. Animals were given the doses of 0.08, 0.4, 2.0, 10 and 50 mg/kg of the compound(I), 0.08, 0.4 and 2.0 mg/kg of hydrocortisone 17-butyrate, and 0.08, 0.4 and 2.0 mg/kg of betamethasone once daily, respectively. The animals serving as a control were administered 5% gum arabic for the same period. There were fatal cases in the males and females given 50 mg/kg of the compound(I). In all aminals treated by any test compound, as the dose level increased, such changes as depression of body weight gains, decreases in WBC count, increases in total cholesterol amount, and decreases in the thymus, adrenal, spleen and mesenteric lymphonodi weight were evident, and the atrophy of the thymus, adrenal, spleen and mesenteric lymphonodi were remarkable when examined histopathologically. At the same dosage level, changes produced by betamethasone 17-valerate were severer than those by others. In the urinalysis, no changes were seen in the treated groups as compared with the control group. And, in the recovery test performed 30 days after the termination of the drug administration, changes of the organs have almost recovered.

It was concluded that the subacute toxicity of steroids by subcutaneous administration was in the following order: betamethason 17-valerate > hydrocortisone 17-butyrate ≧ compound(I).

The present invention is further illustrated by the following detailed example.

EXAMPLE

(1) A solution of hydrocortisone (5 g) in dimethylformamide (5 ml) containing ethyl orthobutyrate (5 ml) and p-toluenesulfonic acid (200 mg) was heated with stirring at 110° C. for 3 hours. To the reaction mixture pyridine (3 ml) was added. After evaporation of the solvent the residue was purified by column chromatography over silica gel and recrystallization from acetone-n-hexane to yield hydrocortisone 17, 21-cyclic ethyl orthobutyrate (3 g). m.p. 166°–167° C.

(2) A solution of hydrocortisone 17, 21-cyclic ethyl orthobutyrate (2.5 g) in methanol (200 ml) containing saturated aqueous oxalic acid (2.5 ml) was allowed to stand at room temperature overnight. After the reaction was complete, the mixture was purified by column chromatography on silica gel with chloroform and recrystallization from acetone-n-hexane to give hydrocortisone 17-butyrate (1.2 g). m.p. 208°–210° C.

(3) To a solution of hydrocortisone 17-butyrate (1.0 g) in pyridine (5 ml) propionic acid anhydride (2 ml) was added at 0° C., and the mixture was allowed to stand at room temperature overnight. The reaction mixture was poured into ice-water (100 ml) and extracted with chloroform. The chloroform solution was washed with dil. HCl and water and dried over anhydrous sodium sulfate. Evaporation of the chloroform and recrystallization of the residue from benzene-n-hexane gave colorless crystals (1 g), m.p. 79°–84° C. Moreover, a solution of these crystals in ethanol was added dropwise to water with stirring, and the precipitate formed was filtrated and dried over phosphorus pentoxide in vacuo at room temperature to give hydrocortisone 17-butyrate 21-propionate as colorless crystalline powders, m.p. 117°–117.5° C. (decomp. at 265°–268° C.).

NMR: (in C_5D_5N); 1.00(3H, s), 1.00–1.30(6H, m), 1.43(3H, s), 4.48(1H, m), 4.74(2H, d.d., J=18 Hz, 6 Hz), 5.65(1H, s).

What we claim is:

1. 17α-butyryloxy-11β-hydroxy-21-propionyloxy-4-pregnen-3,20-dione.

* * * * *

IN THE UNITED STATES PATENT AND TRADEMARK OFFFICE

In re U.S. Patent No. 4,290,962

Issued: September 22, 1981

To: Yasuhide Tachi; Kazuhiko Michishita;
Jozi Nakagami; Jiro Sawada;
Mitsunori Washitake; and
Yoshiaki Kamano

For: NOVEL HYDROCORTISONE DERIVATIVE

* * * * *

DECLARATION OF PAUL E. WHITE, JR.

Hon. Commissioner of Patents & Trademarks
Washington, D.C. 20231

Sir:

Paul E. White, Jr. as patent counsel for Taisho Pharmaceutical Co. Ltd., the assignee of record of the above-identified patent (hereinafter "Applicant"), declares as follows:

(1) That he is a Registered Patent Attorney and partner with the firm of Pillsbury Madison & Sutro LLP, Cushman Darby & Cushman Intellectual Property Group, 1100 New York Avenue, N.W., Ninth Floor, East Tower, Washington, D.C. 20005-3918, authorized to practice before the United States Patent and Trademark Office under Registration No. 32,011, and that he is authorized by Applicant to file the accompanying APPLICATION FOR EXTENSION OF PATENT TERM UNDER 35 U.S.C. § 156, and to execute this Declaration.

(2) That, upon information and belief, Applicant is the assignee of the entire right, title and interest in United States Patent No. 4,290,962, issued September 22, 1981 (hereinafter "the Patent") by reason of an assignment recorded in the United States Patent and Trademark Office on March 3, 1981 at Reel 3830, Frame 0135.

(3) That submitted herewith is an APPLICATION FOR EXTENSION OF PATENT TERM UNDER 35 U.S.C. § 156 for the Patent (hereinafter referred to as the "Application") requesting a three year (1,096 days) extension of the term of the Patent.

(4) That he has reviewed and understands the contents of the Application being submitted pursuant to 37 C.F.R. § 1.740.

(5) That he believes the Patent is subject to extension pursuant to 37 C.F.R. § 1.710.

(6) That he believes an extension of three years (1,096 days) as requested in the Application is justified under 35 U.S.C. § 156 and the applicable regulations.

(7) That he believes the Patent for which the extension is being sought meets the conditions for extension of the term of a patent as set forth in 37 C.F.R. § 1.720.

He declares further that all statements made herein of his own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements are made with the knowledge that willful false statements and the like are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of United States Patent No. 4,290,962, issued September 22, 1981, and any extensions thereof.

Apr. 25, 1997
Date: April 25, 1997

Paul E. White, Jr.
Reg. No. 32,011

IN THE UNITED STATES PATENT AND TRADEMARK OFFFICE

In re U.S. Patent No. 4,290,962

Issued: September 22, 1981

To: Yasuhide Tachi; Kazuhiko Michishita;
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Yoshiaki Kamano

For: NOVEL HYDROCORTISONE DERIVATIVE

* * * * *

CERTIFICATION

Hon. Commissioner of Patents & Trademarks
Washington, D.C. 20231

Sir:

The undersigned hereby certifies that this APPLICATION FOR EXTENSION OF PATENT TERM UNDER 35 U.S.C. § 156, including THE EXHIBITS and supporting papers, are being submitted as duplicate originals.

April 25, 1997
Date: April 25, 1997

Paul E. White, Jr.
Reg. No. 32,011

IN THE UNITED STATES PATENT AND TRADEMARK OFFFICE

In re U.S. Patent No. 4,290,962 Copy No. 2

Issued: September 22, 1981

Box Patent Ext.

To: Yasuhide Tachi; Kazuhiko Michishita;
Jozi Nakagami; Jiro Sawada;
Mitsunori Washitake; and
Yoshiaki Kamano

For: NOVEL HYDROCORTISONE DERIVATIVE

* * * * *

April 25, 1997

SUBMISSION OF APPLICATION FOR EXTENSION OF PATENT TERM UNDER 35 U.S.C. §156

Hon. Commissioner of Patents & Trademarks
Washington, D.C. 20231

Sir:

Submitted herewith are the following papers in support of an application for extension of patent term pursuant to 35 U.S.C. § 156 with respect to the subject patent, filed on behalf of Taisho Pharmaceutical Co., Ltd., a corporation organized under the laws of Japan, having its principal office and place of business in Tokyo, Japan (hereinafter "Applicant"), which is the owner of all right, title and interest in said patent:

1. Power of Attorney from Taisho Pharmaceutical Co., Ltd. to, *inter alia*, the undersigned. (It should be noted that the Power of Attorney submitted with original Copy No. 1 of these papers is the originally executed Power of Attorney.)

2. Application for Extension of Patent Term Under 35 U.S.C. § 156, including:

   Exhibit 1 - Package insert describing the approved product; and

   Exhibit 2 - Copy of the subject patent.

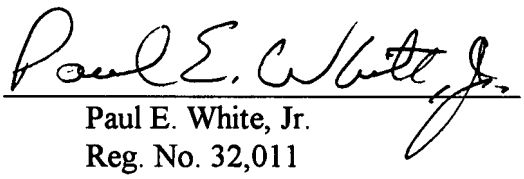
3. Declaration of Paul E. White, Jr., Applicant's patent counsel.

4. Certificate that these application papers are being submitted in duplicate.

5. Check in the amount of $1,090.00 (37 C.F.R. § 1.20(j)(1)) payable to the Commissioner of Patents and Trademarks to cover the prescribed fee.

Respectfully submitted,

CUSHMAN DARBY & CUSHMAN
Intellectual Property Group of
PILLSBURY MADISON & SUTRO, LLP

By: 

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IN THE UNITED STATES PATENT AND TRADEMARK OFFFICE

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* * * * *

POWER OF ATTORNEY FROM ASSIGNEE

Hon. Commissioner of Patents & Trademarks
Washington, D.C. 20231

Sir:

The undersigned Taisho Pharmaceutical Co., Ltd. being the assignee of record in the above-identified patent, hereby appoints Paul E. White, Jr. (Reg. No. 32,011), Paul N. Kokulis (Reg. No. 16,773) and Donald J. Bird (Reg. No. 25,323) of the firm Pillsbury Madison & Sutro, L.L.P. (Cushman Darby & Darby Intellectual Property Group), Ninth Floor, 1100 New York Avenue, N.W., Washington D.C. 20005-3918, telephone number (202) 861-3000 (to whom all communications about this patent are to be directed), individually and collectively, our attorneys to transact all business in the Patent and Trademark Office in connection therewith, including specifically, but not limited to, the filing on our behalf of any application for extension of the patent term thereof under 35 USC 156.

TAISHO PHARMACEUTICAL CO., LTD.
Assignee

By _____
Name: Akira Uehara
Title: President

April 14, 1997
Date